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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,545	05/26/2006	Mark Matteucci	021305-003900US	1659

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EXAMINER	
SHIAO, REI TSANG	
ART UNIT	**PAPER NUMBER**
1626	

MAIL DATE	DELIVERY MODE
07/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,545	MATTEUCCI ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,17-19,21,22,24,26,29,39,41,53-55,64 and 88-98* is/are pending in the application.

4a) Of the above claim(s) *1-5,17-19,21,22,24,26,29,39,41, 64, and 94-98* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-55 and 88-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/22/07, 11/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application claims benefit of the provisional applications: 60/458,845 with a filing date 03/28/2003; and 60/465,281 with a filing date 04/21/2003.

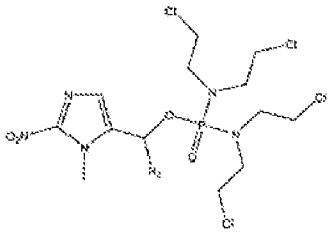
2. Claims 1-5, 17-19, 21, 22, 24, 26, 29, 39, 41, 53-55, 64 and 88-98 are pending in the application.

Information Disclosure Statement

3. Applicant's Information Disclosure Statements filed on October 22, 2007 and November 21, 2006 have been considered. Please refer to Applicant's copies of the 1449's submitted herein.

Responses to Election/Restriction

4. Applicant's election of Group VI claims 53-55 and 88-93, in part, in the reply filed on June 03, 2008, is acknowledged. Election of a compound, i.e.,

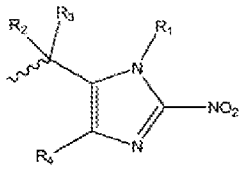


, wherein R3 is hydrogen, as a single species is also acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-5, 17-19, 21, 22, 24, 26, 29, 39, 41, 53-55, 64 and 88-98 are pending in the application. The scope of the invention of the elected subject matter is as follows.

Claims 53-55, and 88-93, in part, drawn to product (i.e., protected anti-neoplastic agent), wherein the variable Hyp (i.e., hypoxic activator) is select from



thereof, and the alkylating agent (i.e., anti-neoplatic agent) is selceted from the group consisting of cyclophosphamide, ifosfamide, melphalan, chlorambucil, thiotepa, cisplatin, and carboplatin.

Claims 53-55, and 88-93, in part, embraced in above elected subject matter, are prosecuted in the case. Claims 53-55, and 88-93, in part, not embraced in above elected subject matter, and claims 1-5, 17-19, 21, 22, 24, 26, 29, 39, 41, 64 and 94-98 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The requirement is still deemed proper and therefore is made FINAL.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 53-55, and 88-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 53-55 and 88-89 respectively recite the limitation “anti-neoplatic agent”, hypoxic activator” and “alkylating agent” is indefinite and ambiguous. It is unclear what the scope of “anti-neoplastic agent”, hypoxic activator” and “alkylating agent” are. The range of “anti-neoplastic agent”, hypoxic activator” and “alkylating agent” of claims 53-55 and 88-89 is from any anti-neoplastic agent or ifosfamide or melphalan. Such breath in view of the limited exemplification and the lack of scope of subject matter resulted from a search of the prior art indicated that the “scope” of claims 53-55 and 88-89 can not be ascertained. In view of the high degree of unpredictability of the chemical art and “anti-neoplastic agent”, hypoxic activator” and “alkylating agent” must be made available at the time the invention was made, i.e., filing of application, the broad scope can not be supplemented with future discovery of new “anti-neoplastic agent”, hypoxic activator” and “alkylating agent”. It is recommended that “anti-neoplastic agent”, hypoxic activator” and “alkylating agent” be limited to the specific disclosure of compound, i.e., see above paragraph 4.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 88 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using alkylating agent of anti-neoplastic agent for treating ovarian cancer does not reasonably provide enablement of alkylating agent of

anti-neoplastic agent (e.g., cyclophosphamide, ifosfamide, melphalan, chlorambucil, thiotepa, cisplatin, and carboplatin) for treating cancer without limitation, see claim 88. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case:

The nature of the invention

The nature of the invention of claim 88 are drawn to intent methods of use using alkylating agent of anti-neoplastic agent (e.g., cyclophosphamide, ifosfamide,

melphalan, chlorambucil, thiotepa, cisplatin, and carboplatin) for treating cancer without limitation (i.e., no named cancer).

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face. The Web site: http://en.wikipedia.org/wiki/Ifosfamide discloses Ifosfamide for treating ovarian cancer.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833,166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Applicants are claiming intent methods of use using alkylating agent of anti-neoplastic agent effective to “cancer” without limitation (i.e., no named cancer). As such, the specification fails to enable the skilled artisan to use the compounds of claims effective to “treat cancer” without limitation (i.e., no named cancer).

In addition, there is no established correlation between *in vitro* or in *vivo* activity and accomplishing treatment of “treating cancer” without limitation (i.e., no named

cancer), and those skilled in the art would not accept allegations in the instant specification to be reliable predictors of success, and those skilled in the art would not be able to use alkylating agent of anti-neoplastic agent since there is no description of an actual method wherein "treating cancer" without limitation in a host is treated.

Hence, one of skill in the art is unable to fully predict possible results from the administration of the alkylating agent of anti-neoplastic agent of claim 88 due to the unpredictability of the "treating cancer" without limitation (i.e., no named cancer). The "treating cancer" without limitation (i.e., no named cancer) is known to have many obstacles that would prevent one of ordinary skill in the art from accepting treating regimen on its face.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the listing of named alkylating agents for treating ovarian cancer, see section [165] on page 45 of the specification. There are no *in vitro* or *in vivo* working examples present for the treatment of any cancer without limitation by the administration of the instant invention.

The breadth of the claims

The breadth of the claims is methods of use of the instant compounds effective to "treating cancer" without limitation (i.e., no named cancer).

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what "treating cancer" without limitation would be benefited (i.e., treated) by the administration of the instant alkylating agents of the instant invention and would furthermore then have to determine which of the claimed methods of use would provide treatment of a disease, if any.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which methods of use exhibit the desired pharmacological activity and which diseases would benefit from this activity. Thus, the specification fails to provide sufficient support of the broad use of the pharmaceutical compounds of the instant claims for the "treating cancer" without limitation.

As a result necessitating one of skill to perform an exhaustive search for which "treating cancer" without limitation, can be treated by what pharmaceutical compounds of the instant claims in order to practice the claimed invention. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds in regards to the treatment of the many diseases resulting from "modulating SIP receptors" without limitation, one

having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation, with no assurance of success. This rejection can be overcome by incorporation of the named cancers (e.g., ovarian cancer) into claim 88 would obviate the rejection.

Claims Objection

7. Claims 53-55, and 88-93 are objected to as containing non-elected subject matter, i.e., anti-neoplatic agent, hypoxic activator, electron deficient nitrobenzene moieties, electron deficient nitrobenzoic acid amide moieties, nitroazole moieties, nitroimidazole moieties, nitrothiophene moieties, nitrothiazole moieties, nitrooxazole moieties, nitrofuran moieties, and nitropyrrole moieties, adrenocortical suppressants, alkylating agents, anthracyclines, antibiotics, antimetabolites, aromatase inhibitors, bisphosphonates, cyclo-oxygenase inhibitors, estrogen receptor modulators, folate antagonists, inorganic aresenates, methylhydrazine derivatives, microtubule

polymerization perturbers,modifiers, nitrosoureas, nucleoside analogs, osteoclast inhibitors, platinum containing compounds, retinoids, substituted ureas, topoisomerase 1 inhibitors, topoisomerase 2 inhibitors, and tyrosine kinase inhibitors, etc. It is suggested that applicants amend the claims to the scope of the elected subject matter as defined on the pages 2-3 *supra*.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rei-tsang Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information

system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO /

Rei-tsang Shiao, Ph.D.
Primary Patent Examiner
Art Unit 1626

July 22, 2008

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/549,545	MATTEUCCI ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	